The structure of macroprolactin is variable, and the reaction of PRL assays with macroprolactin is also variable. The Bayer/Chiron PRL assays may react strongly with the macroprolactin in some patient samples, and concordance of results with other assays does not exclude macroprolactin as a cause of hyperprolactinemia. PEG interferes in the Bayer/Chiron PRL assays, and further work is needed to (a) establish the prevalence of macroprolactin as a cause of hyperprolactinemia, and (b) develop a method for detecting macroprolactin in these assays.

The distribution of specimens containing macroprolactin through UKNEQAS has provided valuable information on the response of PRL assays to macroprolactin. This distribution has also heightened awareness of macroprolactin and encouraged laboratories to consider and investigate macroprolactin as a possible cause of hyperprolactinemia. In the most recent distribution, 49% of respondents considered macroprolactin as a potential cause of hyperprolactinemia, and 5% of respondents who used assays that reacted strongly with the macroprolactin investigated and detected the presence of macroprolactin. Greater awareness of the problem is still required, but considerable progress has been made.

References

Michael N. Fahie-Wilson
Department of Clinical Chemistry
Southend Hospital
Prittlewell Chase
Westcliff-on-Sea
Essex SS0 0RY
United Kingdom
Fax 44-1702-221059
E-mail fhie-wilson@hospital.southend.nhs.uk

Dr. John responds:

To the Editor:
Fahie-Wilson and major equipment manufacturers have done valuable work, but more than one-half of all participants failed to recognize that macroprolactin could be a cause of hyperprolactinemia. New assays are needed that react only with monomeric prolactin. Some prolactin assays are already minimally affected by the presence of macroprolactin (1). Interferences in immunoassays remain important and put patients at risk of unnecessary surgical intervention (2). Continued refinement of prolactin immunoassays is needed.

References

Rhys John
Department of Medical Biochemistry
University College of Wales
Heath Park
Cardiff CF14 4XW
United Kingdom
Fax 44-29-20748383
E-mail rhys.john@cardiffandvale.wales.nhs.uk

MMP1 and MMP3 Polymorphisms in Promoter Regions and Cancer

To the Editor:
Tumors spread by way of a multistep process in which degradation of the extracellular matrix and basement membrane barriers is a key feature. The matrix metalloproteinases (MMPs) comprise a family of at least 16 proteolytic enzymes that degrade the extracellular matrix in a substrate-specific manner and are thought to have important roles in tumor invasion and metastasis (1).

Overexpression of MMPs is associated with tumor invasion and metastasis (2). Rutter et al. (3) recently investigated how insertion of a G nucleotide at −1607 bp in the MMP1 promoter sequence affects regulation of the transcription of the gene. Promoters containing this 2G sequence display substantially higher transcriptional activity than 1G promoters. In tumor cell lines, 2G homoyzgotes are found more often than in the general population (3). These data have been confirmed in patients affected by ovarian (4) and endometrial (5) cancer.

The MMP stromelysin-1 (MMP3) exhibits several activities that would make it a particularly good tumor
promoter. In addition to degrading numerous extracellular-matrix components, MMP3 can activate gelatinase B and the collag enases and release several cell surface molecules, including E-cadherin, a known contributor to cancer development (6).

Ye et al. (7), who reported the presence of a common polymorphism in the MMP3 promoter that was associated with the progression of atherosclerosis, demonstrated that expression of the MMP3 construct with 6A at the polymorphic site was lower than that for a construct containing 5A.

To confirm the role of the MMP1 polymorphism in ovarian and other cancers and to investigate whether the 5A/6A polymorphism in the MMP3 promoter has any correlation with the progression of cancer, we determined frequencies of both alleles in 164 controls and 160 subjects with cancer (43 with breast cancer, 63 with colorectal cancer, 29 with pulmonary cancer, and 25 with ovarian cancer). All patients and controls were from Italy. Whole blood was collected, and DNA was extracted using a commercially available method (Istagene Matrix; Bio-Rad Laboratories) and amplified. Amplification was confirmed before direct sequencing by an automated capillary electrophoresis DNA sequencer (ABI Prism 310; PE Biosystems).

The frequency of heterozygotes and homozygotes for the 5A allele (5A/5A and 5A/6A), which has higher promoter activity than the 6A allele, was significantly higher among patients with cancer (84.5%), with the exception of the colorectal cancer group (73%), than among individuals without cancer (71%; \( \chi^2 = 6.3428; P < 0.02; \text{Table 1})

Our results suggest that the presence of the 5A polymorphism at the MMP3 promoter may be one of the risk factors for the development and/or progression of cancer, especially mammary in tumors. Colorectal cancers differ from other tumors in both MMP3 and MMP1 polymorphisms. We are conducting a clinical study to investigate the correlation between prognosis of individual cancers and the alleles of these two polymorphic sites and explain the difference between studies for ovarian cancer patients.

### Table 1. Frequency of each genotype of the MMP3 and MMP1 promoters in control subjects and in cancer patients.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Controls (n = 164)</th>
<th>All cancers (n = 160)</th>
<th>Mammary (n = 43)</th>
<th>Colorectal (n = 63)</th>
<th>Ovarian (n = 25)</th>
<th>Pulmonary (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/5 + 5/6</td>
<td>42 + 74 (116)</td>
<td>38 + 90 (128)</td>
<td>15 + 22 (37)</td>
<td>11 + 35 (46)</td>
<td>3 + 19 (22)</td>
<td>9 + 14 (23)</td>
</tr>
<tr>
<td>6/6</td>
<td>48</td>
<td>32</td>
<td>6</td>
<td>17</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>MMP1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/2 + 1/2</td>
<td>36 + 86 (122)</td>
<td>40 + 85 (125)</td>
<td>9 + 26 (35)</td>
<td>23 + 26 (49)</td>
<td>2 + 17 (19)</td>
<td>6 + 16 (22)</td>
</tr>
<tr>
<td>1/1</td>
<td>42</td>
<td>35</td>
<td>8</td>
<td>14</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

\( ^a \) MMP3, all cancers group vs controls: \( P = 0.05 \).

\( ^b \) MMP3, mammary cancer vs controls: \( P < 0.05 \).

### References


Maria Luisa Biondi1*
Olivia Turri1
Simona Levi1
Raffaella Seminati1
Federica Cecchini1
Mara Berrini1
Giorgio Ghilardi2
Emma Guagnellini1

1 Laboratorio di Chimica Clinica e Microbiologia
Azienda Ospedaliera San Paolo
Via di Rudini 8
20142 Milan, Italy

2 Dipartimento di Medicina e Chirurgia e Odontoiatria
Ospedale San Paolo
Clinica Chirurgica Generale
Università degli Studi di Milano
20142 Milan, Italy

*Author for correspondence. Fax 39-0289128221; e-mail laboratorio@hspsanpaolo.mi.it.